REMARKS

Claims 1-31 were pending in the instant application. Claims 15-18, 27, 28, 30, and 31 have been withdrawn from consideration by the Examiner as indicated in the May 23, 2002 Office Action. Applicants have amended the specification to remove embedded hyperlinks and to correct minor typographical errors. Claims 6 and 11 have been canceled without prejudice. Claims 1 and 12 have been amended to remove the exemplary phrases "such as" and "e.g." and the language that immediately follows these phrases. Claims 2, 12, and 24 have been amended to correct minor typographical errors. Claims 2, 7, 12, and 29 have been amended to eliminate reference to non-elected subject matter. Claim 12 also has been amended to change its dependency and for clarity. New claims 32-34 have been added to further define the claimed invention. Support for the amendments and the new claims can be found in the originally filed claims and in the specification. Neither the amendments nor the newly added claims introduce any new matter. Accordingly, their entry is requested. Upon entry of the present Amendment, claims 1-5, 7-10, 12-14, 19-26, 29, and 32-34 will be pending and under examination.

In the May 23, 2002 Office Action, the Examiner acknowledged the Applicants' election with traverse of previously set forth claim Group I and SEQ ID NO: 2. The Examiner made the restriction requirement final. In addition to SEQ ID NO: 2, the Examiner has indicated that she has also included SEQ ID NOS. 3 and 12 for consideration.

Examiner's Objection to the Specification

The Examiner objected to the specification because it contained embedded hyperlinks and/or other form of browser executable code. In response, Applicants have amended the specification such that it does not contain embedded hyperlinks or other form of browser executable code. The specification has also been amended to correct minor typographical errors. Applicants believe that these amendments obviate the Examiner's objections to the specification.

Examiner's Objections to Claims

The Examiner objected to claims 2-12, 24, and 29 for being directed to non-elected subject matter and for containing some minor typographical errors. The Examiner also objected to claim 12 for being of improper dependent form, and for reciting the term "may be substituted." In response, Applicants' have amended claims 2, 7, 12, 24, and 29. Applicants believe that these claim amendments obviate the Examiner's objections.

Examiner's Rejections Under 35 U.S.C. §112

The Examiner rejected claims 1, 11-12, and 19-26 under 35 U.S.C. §112, second paragraph as allegedly being indefinite. With respect to claims 1 and 11-12, the Examiner indicated that the exemplary terms "such as" and "e.g." make unclear whether the limitations that follow are part of the claimed invention.

In response, Applicants have amended claims 1 and 12 to remove the exemplary terms and the language that follows them. New claims 32-34 are directed to the subject matter removed from claims 1 and 12. Claim 11 has been canceled.

The Examiner also rejected claim 1, asserting that it is unclear what the term "hydroxylated synthetic residue" (lines 12-13) encompasses or what distinction is to be made between a "synthetic" amino acid and a "non-natural derivative" of an amino acid. The Examiner further questioned how a synthetic phenylalanine is distinguishable from a naturally occurring phenylalanine. The Examiner also rejected claims 19-26 because they ultimately depend from claim1 and do not, in the Examiner's view, clarify the alleged ambiguity.

In response, Applicants respectfully traverse this ground of the Examiner's rejection. Applicants assert that the terms in the claims are clear as written. For instance, the intent in the use of the term "synthetic amino acid" was to include, for example, synthetic basic amino acids, which would not include naturally occurring basic amino acids, whether natural or synthetic. These distinctions are likewise applicable to the other terms about which the Examiner has raised concern.

Accordingly, Applicants assert that claim 1 satisfies the requirements of 35 U.S.C. §112, second paragraph. Applicants therefore respectfully request that the Examiner reconsider and withdraw the rejection of claims 1, 12, and 19-26.

Examiner's Rejections Under 35 U.S.C. §102(e)

The Examiner rejected claims 11 and 12 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,885,797 (Chen, et al.). The Examiner stated that the reference reveals the sequence of mouse transcription factor I-mf, which contains at positions 203-212 the sequence CCGSGECADC. The Examiner asserted that the sequence is deemed anticipatory for the claimed subject matter because the above protein can be considered a derivative of SEQ ID NO: 2, as it retains the core sequence of SEQ ID NO: 1: CCGXXXCXXC.

In response, Applicants respectfully traverse the Examiner's rejection. Claim 11 has been canceled, rendering its rejection moot. Claim 12, as amended, is directed to a defined derivative, the sequence of which is not in fact disclosed anywhere in the reference cited by the Examiner. The Chen, et al. patent cited by the Examiner, does not, therefore, anticipate claim 12. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(e).

In view of the above amendments and remarks, it is believed that the claims satisfy the requirements of the patent statutes and fully address the Examiner's concerns as set forth in the

Office Action of May 23, 2002. Reconsideration of the instant application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

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Attachments: Marked up copy of amendments.

187A.am1

Marked up copy of specification paragraph beginning at page 1, line 20

Conus is a genus of predatory marine gastropods (snails) which envenomate their prey. Venomous cone snails use a highly developed projectile apparatus to deliver their cocktail of toxic conotoxins into their prey. In fish-eating species such as *Conus magus* the cone detects the presence of the fish using chemosensors in its siphon and when close enough extends its proboscis and fires a hollow harpoon-like tooth containing venom into the fish. This immobilizes the fish and enables the cone snail to wind it into its mouth via an attached filament. For general information on *Conus* and their venom see the website address ~~http://~~grimwade.biochem.unimelb.edu.au/cone/referenc.html. Prey capture is accomplished through a sophisticated arsenal of peptides which target specific ion channel and receptor subtypes. Each *Conus* species venom appears to contain a unique set of 50-200 peptides. The composition of the venom differs greatly between species and between individual snails within each species, each optimally evolved to ~~paralyse~~ paralyze ~~it's~~ its prey. The active components of the venom are small peptides toxins, typically 12-30 amino acid residues in length and are typically highly constrained peptides due to their high density of disulphide bonds.

Marked up copy of specification paragraph beginning at page 2, line 3

The venoms consist of a large number of different peptide components that when separated exhibit a range of biological activities: when injected into mice they elicit a range of physiological responses from shaking to depression. The paralytic components of the venom that have been the focus of recent investigation are the α-, ω- and μ-conotoxins. All of these conotoxins act by preventing neuronal communication, but each targets a different aspect of the process to achieve this. The α-conotoxins target nicotinic ligand gated channels, the μ-conotoxins target the voltage-gated sodium channels and the ω-conotoxins target the voltage-gated calcium channels (Olivera et al., 1985). For example a linkage has been established between α-, αA- & ϕ-conotoxins and the nicotinic ligand-gated ion channel; ω-conotoxins and the voltage-gated calcium channel; μ-conotoxins and the voltage-gated sodium channel; δ-conotoxins and the voltage-gated sodium channel; κ-conotoxins and the voltage-gated potassium channel; conantokins and the ligand-gated

glutamate (NMDA) channel. For a partial list of *Conus* peptides and their amino acid sequences see the website address ~~http://~~pir.georgetown.edu.

Marked up copy of specification paragraph beginning at page 6, line 3

Examples of synthetic aromatic amino acid include, but are not limited to, such as nitro-Phe, 4-substituted-Phe wherein the substituent is C_1-C_3 alkyl, carboxyl, hyrdroxymethyl, sulphomethyl, halo, phenyl, -CHO, -CN, -SO_3H and -NHAc. Examples of synthetic hydroxy containing amino acid, include, but are not limited to, such as 4-hydroxymethyl-Phe, 4-hydroxyphenyl-Gly, 2,6-dimethyl-Tyr and 5-amino-Tyr. Examples of synthetic basic amino acids include, but are not limited to, N-1-(2-pyrazolinyl)-Arg, 2-(4-piperinyl)-Gly, 2-(4-piperinyl)-Ala, 2-[3-(2S)pyrrolininyl)-Gly and 2-[3-(2S)pyrrolininyl)-Ala. These and other synthetic basic amino acids, synthetic hydroxy containing amino acids or synthetic aromatic amino acids are described in Building Block Index, Version 3.0 (1999 Catalog, pages 4-47 for hydroxy containing amino acids and aromatic amino acids and pages 66-87 for basic amino acids; see also ~~http://~~www.amino-acids.com), incorporated herein by reference, by and available from RSP Amino Acid Analogues, Inc., Worcester, MA. Examples of synthetic acid amino acids include those derivatives bearing acidic functionality, including carboxyl, phosphate, sulfonate and synthetic tetrazolyl derivatives such as described by Ornstein et al. (1993) and in U.S. Patent No. 5,331,001, each incorporated herein by reference.

Marked-Up Copy of the Amended Claims

1. (Amended) A substantially pure conotoxin peptide having the general formula I:

Xaa-Xaa_0-Xaa_1-Cys-Cys-Gly-Xaa_2-Xaa_3-Xaa_4-Cys-Xaa_5-Xaa_6-Cys-Xaa_7 (SEQ ID NO:1)

wherein Xaa is *des*-Xaa, Asn, Gln or pyro-Glu; Xaa_0 is *des*-Xaa_0, Gly, Ala, Glu, γ-carboxy-Glu (Gla) Asp, Asn, Ser, Thr, g-Asn (where g is glycosylation), g-Ser or g-Thr; Xaa_1 is Val, Ala, Gly, Leu, Ile,Ser, Thr, g-Asn, g-Ser or g-Thr; Xaa_2 is Phe, Tyr, meta-Tyr, ortho-Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr, Trp (D or L), neo-Trp, halo-Trp (D or L), any synthetic aromatic amino acid, an aliphatic amino acid bearing linear or branched saturated hydrocarbon chains ~~such as Leu (D or L), Ile and Val~~ or a non-natural derivatives of the aliphatic amino acid; Xaa_3 is Lys, Arg, homolysine, homoarginine, ornithine, nor-Lys, His, N-methyl-Lys, N,N'-dimethyl-Lys, N,N',N''-trimethyl-Lys, any synthetic basic amino acid, Ser, Thr, g-Ser, g-Thr or any hydroxylated synthetic residue; Xaa_4 is an aliphatic amino acids bearing linear or branched saturated hydrocarbon chains ~~such as Leu (D or L), Ile and Val~~ or a non-natural derivatives of the aliphatic amino acid, Met, Phe, Tyr, meta-Tyr, ortho-Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr, Trp (D or L), neo-Trp, halo-Trp (D or L) or any synthetic aromatic amino acid; Xaa_5 is His, Ser, Thr, g-Ser, g-Thr, an aliphatic amino acid bearing linear or branched saturated hydrocarbon chains ~~such as Leu (D or L), Ile and Val~~, a non-natural derivatives of the aliphatic amino acid, Phe, Tyr, meta-Tyr, ortho-Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr, Trp (D or L), neo-Trp, halo-Trp (D or L) or a synthetic aromatic amino acid; Xaa_6 is Pro, hydroxy- Pro (Hyp) or g-Hyp; Xaa_7 is *des*-Xaa_7, Gly, Ala, Lys,Arg, homolysine, homoarginine, ornithine, nor-Lys, His, N-methyl-Lys, N,N'-dimethyl-Lys, N,N',N''-trimethyl-Lys or any synthetic basic amino acid; and the C-terminus contains a free carboxyl group or an amide group.

2. (Amended) The substantially pure conotoxin peptide of claim 1 ~~selecected~~ selected from the group consisting of:

Asn-Gly-Val-Cys-Cys-Gly-Xaa$_1$-Xaa$_2$-Leu-Cys-His-Xaa$_3$-Cys (SEQ ID NO:2); and
Gly-Val-Cys-Cys-Gly-Xaa$_1$-Xaa$_2$-Leu-Cys-His-Xaa$_3$-Cys (SEQ ID NO:3);
~~Gly-Ile-Cys-Cys-Gly-Val-Ser-Phe-Cys-Xaa$_1$-Xaa$_5$-Cys (SEQ ID NO:4);~~
~~Ala-Cys-Cys-Gly-Xaa$_1$-Xaa$_2$-Leu-Cys-Ser-Xaa$_3$-Cys (SEQ ID NO:5);~~
~~Xaa$_4$-Thr-Cys-Cys-Gly-Xaa$_1$-Arg-Met-Cys-Val-Xaa$_3$-Cys-Gly (SEQ ID NO:6); and~~
~~Ser-Thr-Cys-Cys-Gly-Phe-Xaa$_2$-Met-Cys-Ile-Xaa$_5$-Cys-Arg (SEQ ID NO:7),~~
wherein Xaa$_1$ is Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr; Xaa$_2$ is Lys, N-methy-Lys, N,N-dimethyl-Lys or N,N,N-trimethyl-Lys; Xaa$_3$ is Pro or hydroxy-Pro~~, preferably hydroxy-Pro; Xaa$_4$ is Gln or pyro-Glu~~; and the C-terminus contains a carboxyl or amide group.

7. (Amended) The substantially pure conotoxin peptide of claim 2, wherein Xaa$_1$ is Tyr, Xaa$_2$ is Lys, and Xaa$_3$ is hydroxy-Pro~~ and Xaa$_4$ is Gln~~.

12. (Amended) ~~The~~A substantially pure conotoxin peptide derivative~~ of claim 11~~ comprising the peptide of claim 2, wherein ~~the Arg residues may be substituted by Lys, ornithine, homoargine, nor-Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any synthetic basic amino acid; the~~at least one amino acid residue is substituted, said substitution being selected from the group consisting of an Xaa$_2$ residues~~ may be~~ substituted by Arg, ornithine, ~~homoargine~~ homoarginine, nor-Lys, or any synthetic basic amino acid;~~ the~~a Tyr residues~~ may be~~ substituted with any synthetic aromatic containing amino acid; ~~the~~a Ser residues~~ may be~~ substituted with Thr or any synthetic hydroxy containing amino acid; ~~the~~a Thr residues~~ may be~~ substituted with Ser or any synthetic hydroxy containing amino acid; ~~the~~ a Phe ~~and Trp~~ residues~~ may be~~ substituted with any synthetic aromatic amino acid; a Trp residue substituted with any synthetic aromatic amino acid; ~~the~~an Asn~~, Ser, Thr or Hyp~~ residues~~ may be~~ glycosylated; a Ser residue glycosylated; a Thr residue glycosylated; a Hyp residue glycosylated;~~the~~ a Cys residues~~ may be~~ in D or L configuration; ~~the~~a Cys residues~~ may be~~ substituted with homocysteine (D or L); ~~the~~a Tyr residues~~ may also be~~ substituted with the 3-

hydroxyl or 2-hydroxyl isomers (meta-Tyr or ortho-Tyr, respectively) and corresponding O-sulpho- and O-phospho-derivatives; ~~the~~an acidic amino acid residues~~ may be~~ substituted with any synthetic acidic amino acid~~, e.g., tetrazolyl derivatives of Gly and Ala~~; a pairs of Cys residues~~ may be~~ replaced pairwise with isoteric lactam or ester-thioether replacements~~, such as Ser/(Glu or Asp), Lys/(Glu or Asp) or Cys/Ala combinations~~; and ~~the~~an aliphatic amino acids~~ may be~~ substituted by synthetic derivatives bearing non-natural aliphatic branched or linear side chains C_nH_{2n+2} up to and including n=8.

24. (Amended) The method of claim 20, wherein the amount of conotoxin peptide~~d~~ administered is between about 0.001 mg/kg to about 250 mg/kg.

29. (Amended) An isolated conotoxin propeptide~~ selected from the group consisting of:~~

~~(a)~~ having the amino acid sequence set forth in SEQ ID NO:12~~;~~

~~(b) the amino acid sequence set forth in SEQ ID NO:14;~~

~~(c) the amino acid sequence set forth in SEQ ID NO:16; and~~

~~(d) the amino acid sequence set forth in SEQ ID NO:18~~.